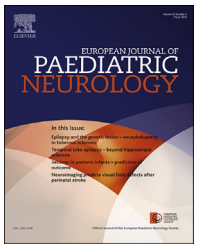
ELSEVIER

Official Journal of the European Paediatric Neurology Society



Original article

The clinical profile of tuberous sclerosis complex (TSC) in the United Kingdom: A retrospective cohort study in the Clinical Practice Research Datalink (CPRD)

Christopher Kingswood [a,*], *Patrick Bolton* [b], *Pamela Crawford* [c], *Christopher Harland* [d], *Simon R. Johnson* [e], *Julian R. Sampson* [f], *Charles Shepherd* [g], *Jayne Spink* [h], *Dirk Demuth* [i], *Lara Lucchese* [i], *Paola Nasuti* [i], *Elizabeth Gray* [j], *Alun Pinnegar* [j], *Matthew Magestro* [k]

[a] *The Royal Sussex County Hospital, Brighton, UK*
[b] *Institute of Psychiatry, Kings College London, London, UK*
[c] *York Hospital, York, UK*
[d] *Epsom and St Helier University Hospitals NHS Trust, UK*
[e] *Queen's Medical Centre, Nottingham, UK*
[f] *Institute of Medical Genetics, Cardiff University School of Medicine, Cardiff, UK*
[g] *Nobles Hospital, Isle of Man, UK*
[h] *Tuberous Sclerosis Association, London, UK*
[i] *IMS Health, London, UK*
[j] *Novartis Pharmaceuticals, UK Ltd, Frimley, UK*
[k] *Novartis Pharmaceuticals Corporation, East Hanover NJ, USA*

ARTICLE INFO

Article history:
Received 28 February 2015
Received in revised form
25 September 2015
Accepted 23 November 2015

Keywords:
Tuberous sclerosis
Subependymal giant cell astrocytoma (SEGA)
Epilepsy
Angiomyolipoma
Retrospective database
Prevalence manifestations

ABSTRACT

Background: Tuberous Sclerosis Complex (TSC) is a multi-system genetic disorder characterised by the development of benign growths and diverse clinical manifestations, varying in severity, age at onset and with high clinical burden.

Aims: This longitudinal study aims to describe the broad spectrum of clinical manifestation profiles in a large, representative cohort of TSC patients in the UK in order to better understand disease complexity.

Methods: TSC patients in the Clinical Practice Research Datalink (CPRD) and linked Hospital Episodes Statistics (CPRD-HES) were retrospectively identified between 1987 and 2013. Available history was extracted for each patient and clinical diagnosis, procedure and medication records reviewed. A random selection of patients from the CPRD-HES was used as a Comparator cohort.

Results: Three hundred and thirty-four TSC patients with a mean (SD) age of 30.3 (18.6) years were identified (53% female). TSC was diagnosed at mean age 3.2 (4.2) years. Epilepsy and psychiatric manifestations were reported frequently in paediatric (77% and 55%, respectively) and adult patients (66% and 68%, respectively). The prevalence

* *Corresponding author.*
E-mail addresses: chriskingswood@me.com, chris.kingswood@bsuh.nhs.uk (C. Kingswood).
http://dx.doi.org/10.1016/j.ejpn.2015.11.011

of manifestations in the TSC cohort was markedly higher versus the Comparator cohort. The majority of paediatric (46%) and adult TSC patients (62%) developed clinical manifestations affecting at least three organ systems and forty-nine distinctive organ system manifestation profiles were identified.

Conclusions: TSC patients present with multiple and complex clinical manifestations and profiles that necessitate the co-ordinated action of a multidisciplinary team in order to improve the quality and efficiency of care.

1. Introduction

Tuberous sclerosis complex (TSC) is a rare genetic disease associated with the development of non-malignant tumours throughout the body. Mutations in the *TSC1* and *TSC2* genes, which encode the proteins hamartin and tuberin,[1–3] are detected in approximately 85–90% of TSC cases.[4–10] The majority of TSC cases occur sporadically, with a family history found in only 30% of patients.[1,6,11–13] The incidence of TSC is estimated to be between 1/6000 and 1/10,000 live births and the population prevalence is estimated to be 1/20,000.[14,15] Approximately 1 in 12,000–14,000 children under 10 years of age have TSC according to population-based studies in the UK.[14,16] Worldwide, TSC is thought to affect 1 to 2 million individuals.

The clinical presentation of TSC is highly variable between individuals and typically varies throughout the lifetime of a single patient, both factors making for a highly heterogeneous presentation of the disease when assessing the patient population cross-sectionally.[13,17] The diverse timing of the onset of manifestations and the symptoms and signs they cause adds to the complexity of the condition. The central nervous system (CNS), dermatological, renal, respiratory and circulatory organ systems are most commonly affected, although few of these manifestations are specific to TSC.[13,18,19] Infantile spasms are usually the first detected manifestations. Neurodevelopmental and dermatological manifestations also typically present early in life, though are frequently misdiagnosed. Clinical complications from renal manifestations, on the other hand, are often first observed in adolescence or adulthood; although renal involvement can be demonstrated much earlier (age 3–5) and presumably starts even earlier on the microscopic scale. Respiratory system involvement, almost exclusively symptomatic in female TSC patients, typically presents in adults. Ocular and bone abnormalities have been commonly reported but are not diagnostic.[10,18] Other organ systems including the gastrointestinal, hepatic, auditory and endocrine systems are less commonly affected by TSC.[13,18–20]

The diagnosis of TSC can be challenging due to the heterogeneous presentation of the disease. Based on the 2012 International TSC Consensus Group guidelines,[18,21] clinical features of TSC continue to be the principal means of diagnosis with the presence of two major features or one major plus two minor features necessary for a definitive diagnosis. In addition, identification of a pathogenic *TSC1* or *TSC2* mutation by genetic testing is considered an independent diagnostic criterion, although in 10–15% of clinically-affected patients, current testing is not able to identify such a mutation.[18]

Beyond diagnosis, TSC presents the clinical community with challenges in delivering adequate care given the number of organ systems affected by the disease and the age-dependent nature of manifestations. Such challenges were addressed by the consensus group for surveillance and management.[21] Recommendations from this group highlight the need for a holistic and coordinated management approach in order to deliver efficient and effective care for TSC patients throughout their lifetime.

Barriers to improving the quality and coordination of care in TSC are compounded by the lack of long-term studies that collate information across the broad spectrum of manifestations, analyse the combinations of organ systems involved and document the age of onset and progression of clinical features. Previous studies of TSC have focused on defined subsets of the disease, typically in small patient populations, and usually addressing a particular manifestation or organ system. The current study uses a longitudinal database to enhance understanding of the natural history of TSC in a large cohort of paediatric and adult patients in the community setting in the UK. The study describes the broad spectrum and complexity of patient manifestation profiles, including the age-related emergence of clinical features, with the aim of supporting clinicians' diagnosis, surveillance and management of TSC.

By providing a long-term picture of TSC in the community in the UK, this study aims to improve diagnosis, surveillance and management of TSC, and to aid the development of care pathways to improve long-term health outcomes for patients.

2. Methods

2.1. *Study design and data source*

The study was a retrospective cohort analysis of UK patient data from the Clinical Practice Research Datalink (CPRD) linked (via patient National Health Service [NHS] number) to secondary care data from the Hospital Episodes Statistics (CPRD-HES) database and the Office of National Statistics (ONS) mortality register.

The CPRD is an electronic medical record database with longitudinal data available from 1987. Currently, it includes approximately 6 million *active* patients (approximately 15.5 million patients in total) from over 680 primary care practices throughout the UK, representing approximately 8% coverage of the general UK population.[22] The CPRD consists of a number

of data files that capture information on patient demographics, clinical diagnoses, consultations, co-morbidities, prescription medications, routine tests and specialist referrals.[23,24] Diagnoses are assigned by clinicians and recorded using the Oxford Medical Information System classification and Read Clinical Terms. Prescription medications are coded according to the CPRD product code. All data files within the CPRD (except the free-text notes) were reviewed and evaluated for inclusion in the current study.

The HES database provides information on inpatient care (including those patients admitted through the accident and emergency department) delivered by NHS hospitals in England, with data linked to CPRD available from April 1997 to March 2012 (approximately 50% of GP practices in England are linked to HES data). Data including basic demographics, clinical diagnoses (recorded using World Health Organization International Classification of Disease [ICD]-10 codes), procedures (recorded using Office of Population Censuses and Surveys [OPCS] Classification of Interventions and Procedures version 4]) and administrative information (date of admission) are captured in HES. Outpatient attendance data is also captured in HES and was available from April 2003 to March 2012. ONS is part of the Executive Office of the UK Statistics Authority and collects, compiles, analyses and disseminates a range of economic, social and demographic statistics relating to the UK. Linked ONS mortality data was available from January 1998 to January 2012.

The CPRD has been well validated and has previously been used to support the design and implementation of epidemiological cohort studies.[23–28]

2.2. Patient population

Subjects were identified based on a diagnosis of TSC recorded in the CRPD-HES (Read codes, PK5..00, PK5..12; ICD-10 code, Q85.1) from 1st January, 1987 to 30th June, 2013 (the latest date at which data was available at the time of extraction). All patients with a record of TSC in the CPRD for whom linked HES data were available were included in the study, regardless of the length of history available for each patient. Patients with an incorrectly coded TSC diagnosis, as determined by clinician review, were excluded from the study.

All available history was extracted for each TSC patient identified, including demographic (gender and age) and clinical data (diagnoses, symptoms, prescription medication, investigations and procedures, including surgical interventions and imaging tests).

2.3. Data categorisation

Data were aggregated for each patient to construct (to the extent possible) a comprehensive medical history. To accommodate the volume and complexity of records, each diagnosis, procedure and prescription medication was reviewed by a panel of clinical experts to determine the extent to which they were related to TSC. Records were then grouped by affected organ system in a TSC clinical code library — *the Medical Inventory of TSC Organ System Codes (MedITOSC)* — which was used to systematically assess the population (Table 1). Seven *primary* manifestation categories (hereafter referred to as 'primary organ systems') affected by TSC were identified; brain (structural), nervous system, psychiatric, kidney and urinary tract, circulatory system, dermatological and respiratory.

The relationship of manifestations with TSC was further categorised based on having: i) a high degree of certainty of being directly related to TSC (TSC-related); or ii) a likelihood of association with TSC (TSC-associated), either directly or indirectly. Data records considered by the clinical expert panel to be unrelated to TSC were excluded from the analyses.

2.4. Data analyses

Analyses were performed on the entire 'TSC' cohort and on the TSC sub-cohort for whom records were available from birth ('TSC Birth' cohort). A random sample of 100,000 patients from the general CPRD population, with linked HES data, was used as a 'Comparator' cohort for analyses. Demographic

Table 1 – Medical inventory of TSC organ system codes (MedITOSC).

Organ system	Manifestations
Central nervous system (CNS)[a]	• *Brain (Structural)*: Brain neoplasms (including subependymal giant cell astrocytoma [SEGA]), hydrocephalus, cerebral cyst, stroke/transient ischaemic attack (TIA) • *Nervous System:* Epilepsy (including convulsions and any fit; excluding febrile convulsions), ataxia/hemiplegia • *Psychiatric*: Learning/intellectual disability, autism spectrum disorders, sleep disorder, hallucinations, behavioural disorder, speech and language disorders, attention deficit hyperactivity disorder (ADHD), bipolar disorder, depression, anxiety, psychosis/schizophrenia, dysphasia/aphasia, anorexia
Kidney and urinary tract[a]	• Polycystic kidney disease, kidney cyst, chronic kidney disease stage 3–5, kidney neoplasms (including angiomyolipomas), haematuria
Circulatory system[a]	• Cardiac rhabdomyoma, hypertension, arrhythmia, myocardial infarction/angina, cerebral/cardiac aneurysm[b]
Dermatological[a]	• Angiofibroma, benign skin neoplasms, naevus, acne vulgaris/rosacea, café au lait spots, rhinophyma, nail manifestations, skin tag, impetigo, other skin-related lesions, lymphoedema
Respiratory[a]	• Lymphangioleiomyomatosis (LAM)[c]
Ocular	• Visual impairment (including partial sight, poor visual acuity, registered blind, unspecified visual loss, loss of vision, deteriorating vision)
gastrointestinal system	• Benign neoplasms/polyp of colon
Endocrine system	• Hyperthyroidism, hypothyroidism

[a] Primary organ system.
[b] Hypomelanotic lesions were not captured by coding.
[c] Suspected cases of LAM only due to unavailability of specific LAM diagnosis codes in CPRD-HES.

characteristics, including gender and age (defined at the point of the last available record for each patient), are reported consistently for TSC and Comparator cohorts.

The frequency of TSC-related and TSC-associated clinical manifestations in the TSC cohort was analysed by individual manifestation and by organ system, and further stratified by paediatric (<18 years) and adult (≥18 years) patients. The frequency of select clinical manifestations was also compared with the Comparator cohort by age intervals in order to account for the development of some manifestations later in adulthood.

Data are presented as summary statistics where continuous variables are presented as mean, standard deviation (SD) and median values and categorical variables are reported as frequencies and percentages along with 95% confidence intervals, where appropriate. Statistical analysis was performed using SAS® version 9.2.

2.5. Ethics

Independent Scientific Advisory Committee (ISAC) for Medicine and Healthcare Products Regulatory Agency (MHRA) Database Research approval was obtained for this study on 2nd September 2013 (Protocol 13_146).

3. Results

3.1. Patient demographics

A total of 334 patients with a TSC diagnosis were identified in the CPRD-HES database (TSC cohort). The TSC cohort had a mean (SD) available history of 17.4 (6.4) years (median, 18.7 years), a slightly higher proportion of females (53%) and a mean age of 30.3 (18.6) years, based on the patients' last available record. The age distribution of the TSC cohort is shown in Fig. 1. The majority (65%) of patients were under the age of 35 years; only 11% of patients were over 55 years of age.

Demographics in the TSC cohort were compared with those in the Comparator cohort in order to establish any differences with the general CPRD population. Mean (SD) available follow-up in the Comparator cohort was similar to that observed in the TSC cohort (15.7 [7.2] years; median, 16.8 years) as was the gender distribution (57% female). In contrast, the mean age of patients in the Comparator cohort was markedly higher (43.1 [25.6] years) versus the TSC cohort, with a substantially greater proportion of patients (42%) over the age of 55 years (Fig. 1).

3.2. Prevalence of TSC clinical manifestations by primary organ system

As clinical manifestations are known to develop at different times throughout the disease course, the prevalence of TSC-related and TSC-associated manifestations by primary organ system were analysed separately for paediatric and adult patients in the TSC cohort (Fig. 2). Over three quarters of paediatric patients developed nervous system manifestations (predominantly epilepsy) and one in every two patients developed a psychiatric manifestation. Manifestations impacting the circulatory system were also prevalent in the paediatric TSC cohort, developing in nearly one quarter (23%) of patients, while 13% were reported to show structural manifestations of the brain excluding tubers. The prevalence of nervous system and psychiatric manifestations remained high in the adult TSC cohort (66% and 68%, respectively). Kidney and urinary tract manifestations were primarily reported later in adult life (34% *vs.* 4%, paediatric TSC cohort). Dermatological manifestations were prevalent in the majority of the paediatric and adult TSC cohort (69% and 81%, respectively). Respiratory manifestations were identified in less than 2% of adult TSC patients.

3.3. Comparison of prevalence of clinical manifestations in the TSC cohort versus the comparator cohort

The prevalence of TSC-related and TSC-associated manifestations was examined separately in the TSC cohort for paediatric and adult patients (Tables 2A and 2B) and compared with the Comparator cohort (Table 2A). For the majority of manifestations compared, prevalence was markedly higher in the TSC cohort than in the Comparator cohort, with depression the only exception (occurring at similar frequencies at each age interval). In comparison with the Comparator cohort, paediatric TSC patients were shown to have a higher prevalence of brain neoplasms (11% *vs.* 0%), epilepsy (77% *vs.* 3%), autism spectrum disorders (16% *vs.* 1%), attention deficit hyperactivity disorder (ADHD; 7% *vs.* 1%), learning/intellectual disability (34% *vs.* 1%) and cardiac rhabdomyomas (19% *vs.* 0%). In the TSC cohort, the prevalence of kidney neoplasms was also markedly higher than that observed in the Comparator cohort, with the highest prevalence observed at 56–65 years (21% *vs.* 0%). Chronic kidney disease (CKD stage 3–5) was also identified more frequently in the TSC cohort compared with the Comparator cohort at all age intervals and peaked at >65 years of age (42% *vs.* 23%). A higher prevalence of stroke/transient ischaemic attack (TIA) was observed in the TSC cohort compared with the Comparator cohort (Table 2A).

The prevalence of visual impairment and hypothyroidism/hyperthyroidism, less commonly reported clinical manifestations,[18,29] were also markedly higher in the TSC cohort than in the Comparator cohort at all age intervals (Table 2A). Prevalence of visual impairment peaked at 46–55 years (7% *vs.* 1%), while diagnosis of hypothyroidism/hyperthyroidism was most prevalent at ages 56–65 years (37% *vs.* 7%). Furthermore, a higher prevalence of impetigo and lymphoedema was observed in adult TSC patients relative to the Comparator cohort (Table 2A).

3.4. Age at first diagnosis of TSC manifestations

To gain insight into when TSC clinical manifestations develop, age at first diagnosis of select manifestations ($n \geq 5$) by primary organ system was reported in the TSC Birth cohort (Fig. 3). Cardiac rhabdomyomas followed by epilepsy were the earliest detected manifestations, with the former commonly diagnosed within the first year of life (mean [SD]; 0.8 (1.4) and 2.1 [3.4] years of age, respectively). On average, psychiatric manifestations were also initially diagnosed at a relatively young age (<10 years), including sleep disorders, speech and

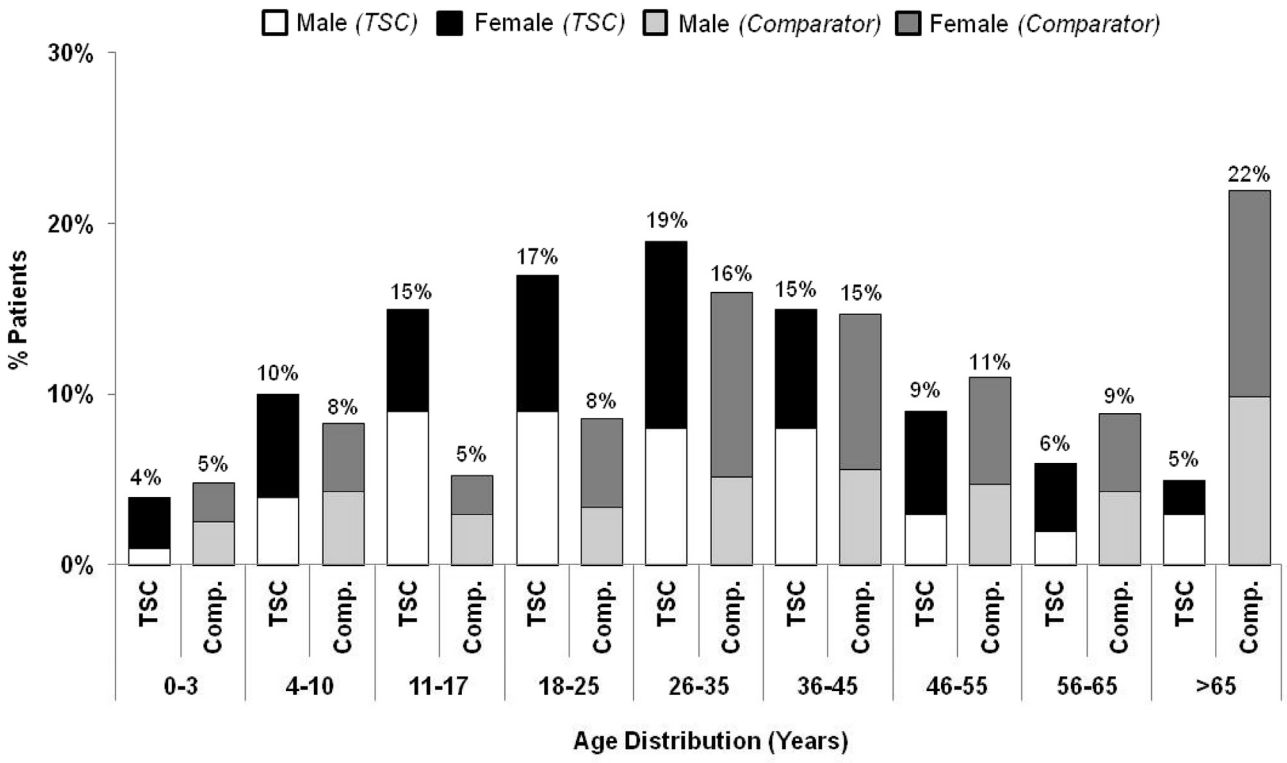


Fig. 1 – Age distribution by gender of the TSC cohort (n = 334) versus the Comparator cohort (n = 100,000). Age defined at the point of the last available record for each patient.

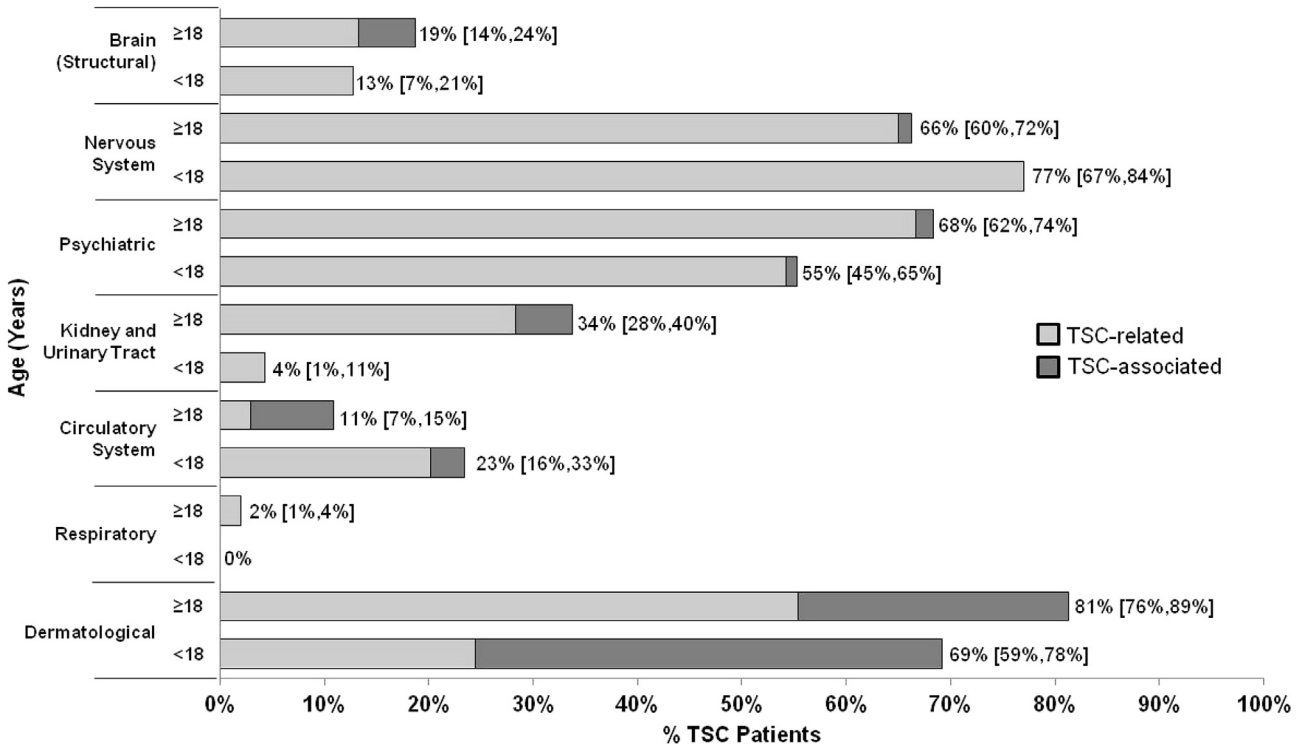


Fig. 2 – Comparison of prevalence (95% confidence intervals) of clinical manifestations (TSC-related and TSC-associated) by primary organ system in paediatric (n = 94) versus adult (n = 240) patients in the TSC cohort. Age defined at the point of the last available record for each patient.

Table 2A – Prevalence of select clinical manifestations in the TSC cohort versus the Comparator cohort.

TSC clinical manifestations		<18 yrs[a] TSC n = 94 Comp. n = 18,321		18–25 yrs[a] TSC n = 59 Comp. n = 8326		26–35 yrs[a] TSC n = 62 Comp. n = 15,800		36–45 yrs[a] TSC n = 51 Comp. n = 14,733		46–55 yrs[a] TSC n = 30 Comp. n = 10,834		56–65 yrs[a] TSC n = 19 Comp. n = 9051		>65 yrs[a] TSC n = 19 Comp. n = 22,935	
		n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Brain (Structural)															
Brain Neoplasms	TSC	10	10.6(5.2–18.7)	12	20.3(11.032.8)	9	14.5(6.9–25.8)	4	7.8(2.2–18.9)	0	–	2	10.5(1.3–33.1)	0	–
(inc. SEGA)[b]	Comp.	8	0.0(0.0–0.1)	9	0.1(0.0–0.2)	12	0.1(0.0–0.1)	26	0.2(0.1–0.2)	32	0.3(0.2–0.4)	32	0.4(0.2–0.5)	71	0.3(0.2–0.4)
Cerebral Cyst	TSC	0	–	2	3.4(0.4–11.7)	1	1.6(0.0–8.7)	1	2.0(0.1–10.5)	0	–	0	–	0	–
	Comp.	6	0.0(0.0–0.1)	4	0.0(0.0–0.1)	8	0.1(0.0–0.1)	8	0.1(0.0–0.1)	8	0.1(0.0–0.1)	6	0.1(0.0–0.1)	14	0.1(0.0–0.1)
Stroke/TIA[b]	TSC	1	1.1(0.0–5.8)	0	–	0	–	3	5.9(1.2–16.2)	2	6.7(0.8–22.1)	4	21.1(6.1–45.6)	4	21.1(6.1–45.6)
	Comp.	10	0.1(0.0–0.1)	6	0.1(0.0–0.1)	11	0.1(0.0–0.1)	65	0.4(0.3–0.5)	135	1.2(1.0–1.5)	295	3.3(2.9–3.6)	3004	13.1(12.7–13.5)
Nervous System															
Epilepsy	TSC	72	76.6(66.7–84.7)	43	72.9(59.7–83.6)	43	69.4(56.4–80.4)	34	66.7(52.1–79.2)	18	60.0(40.6–77.3)	14	73.7(48.8–90.9)	7	36.8(16.3–61.6)
	Comp.	458	2.5(2.3–2.7)	314	3.8(3.4–4.2)	439	2.8(2.5–3.0)	451	3.1(2.8–3.3)	442	4.1(3.7–4.5)	318	3.5(3.1–3.9)	972	4.2(4.0–4.5)
Psychiatric															
ADHD[b]	TSC	7	7.4(3.1–14.7)	2	3.4(0.4–11.7)	0	–	0	–	1	3.3(0.1–17.2)	0	–	0	–
	Comp.	192	1.0(0.9–1.2)	142	1.7(1.4–2.0)	39	0.2(0.2–0.3)	6	0.0(0.0–0.1)	3	0.0(0.0–0.1)	1	0.0(0.0–0.0)	5	0.0(0.0–0.0)
Autism Spectrum	TSC	15	16.0(9.2–25.0)	13	22.0(12.3–34.7)	7	11.3(4.7–21.9)	1	2.0(0.1–10.5)	3	10.0(2.1–26.5)	2	10.5(1.3–33.1)	0	–
Disorders	Comp.	181	1.0(0.8–1.1)	89	1.1(0.8–1.3)	25	0.2(0.1–0.2)	25	0.2(0.1–0.2)	6	0.1(0.0–0.1)	6	0.1(0.0–0.1)	4	0.0(0.0–0.0)
Bipolar Disorder	TSC	0	–	1	1.7(0.0–9.1)	2	3.2(0.4–11.2)	0	–	0	–	0	–	0	–
	Comp.	1	0.0(0.0–0.0)	10	0.1(0.0–0.2)	56	0.4(0.3–0.4)	71	0.5(0.4–0.6)	45	0.4(0.3–0.5)	35	0.4(0.3–0.5)	68	0.3(0.2–0.4)
Depression	TSC	0	–	7	11.9(4.9–22.9)	13	21.0(11.7–33.2)	23	45.1(31.1–59.7)	8	26.7(12.3–45.9)	6	31.6(12.6–56.6)	8	42.1(20.3–66.5)
	Comp.	69	0.4(0.3–0.5)	1215	14.6(13.8–15.4)	3311	21.0(20.3–21.6)	4025	27.3(26.6–28.0)	3718	34.3(33.4–35.2)	3378	37.3(36.3–38.3)	8517	37.1(36.5–37.8)
Learning/Intellectual	TSC	32	34.0(24.6–44.5)	23	39.0(26.6–52.6)	30	48.4(35.5–61.4)	19	37.3(24.1–51.9)	8	26.7(12.3–45.9)	9	47.4(24.5–71.1)	7	36.8(16.3–61.6)
Disability	Comp.	145	0.8(0.7–0.9)	155	1.9(1.6–2.2)	127	0.8(0.7–0.9)	92	0.6(0.5–0.8)	84	0.8(0.6–0.9)	73	0.8(0.6–1.0)	72	0.3(0.2–0.4)
Speech and Language	TSC	10	10.6(5.2–18.7)	4	6.8(1.9–16.5)	5	8.1(2.7–17.8)	8	15.7(7.0–28.6)	6	20.0(7.7–38.6)	3	15.8(3.4–39.6)	1	5.3(0.1–26.0)
Disorders	Comp.	409	2.2(2.0–2.4)	213	2.6(2.2–2.9)	96	0.6(0.5–0.7)	59	0.4(0.3–0.5)	67	0.6(0.5–0.8)	89	1.0(0.81.2)	326	1.4(1.3–1.6)
Kidney &Urinary Tract															
Kidney Neoplasms	TSC	3	3.2(0.7–9.0)	6	10.2(3.8–20.8)	11	17.7(9.2–29.5)	9	17.6(8.4–30.9)	6	20.0(7.7–38.6)	4	21.1(6.1–45.6)	1	5.3(0.1–26.0)
(inc. Angiomyolipoma)	Comp.	0	–	1	0.0(0.0–0.0)	1	0.0(0.0–0.0)	1	0.0(0.0–0.0)	1	0.0(0.0–0.0)	0	–	1	0.0(0.0–0.0)
Chronic Kidney	TSC	1	1.1(0.0–5.8)	1	1.7(0.0–9.1)	4	6.5(1.8–15.7)	4	7.8(2.2–18.9)	9	30.0(14.7–49.4)	6	31.6(12.6–56.6)	8	42.1(20.3–66.5)
Disease	Comp.	32	0.2(0.1–0.2)	30	0.4(0.2–0.5)	103	0.7(0.5–0.8)	204	1.4(1.2–1.6)	307	2.8(2.5–3.1)	599	6.6(6.1–7.1)	5363	23.4(22.8–23.9)
Kidney Cyst	TSC	1	1.1(0.0–5.8)	3	5.1(1.1–14.2)	7	11.3(4.7–21.9)	3	5.9(1.2–16.2)	0	–	1	5.3(0.1–26.0)	1	5.3(0.1–26.0)
	Comp.	4	0.0(0.0–0.0)	8	0.1(0.0–0.2)	8	0.1(0.0–0.1)	13	0.1(0.0–0.1)	23	0.2(0.1–0.3)	30	0.3(0.2–0.4)	242	1.1(0.9–1.2)
Polycystic Kidney	TSC	0	–	3	5.1(1.1–14.2)	5	8.1(2.7–17.8)	3	5.9(1.2–16.2)	0	–	1	5.3(0.1–26.0)	1	5.3(0.1–26.0)
Disease	Comp.	7	0.0(0.0–0.1)	1	0.0(0.0–0.0)	6	0.0(0.0–0.1)	8	0.1(0.0–0.1)	13	0.1(0.1–0.2)	9	0.1(0.0–0.2)	24	0.1(0.1–0.1)
Circulatory System															
Cardiac Rhabdomyoma	TSC	18	19.1(11.8–28.6)	4	6.8(1.9–16.5)	0	–	0	–	0	–	0	–	0	–
	Comp.	0	–	0	–	0	–	1	0.0(0.0–0.0)	0	–	2	0.0(0.0–0.1)	2	0.0(0.0–0.0)
Myocardial Infarction/	TSC	0	–	0	–	0	–	0	–	0	–	2	10.5(1.3–33.1)	4	21.1(6.1–45.6)
Angina	Comp.	3	0.0(0.0–0.0)	5	0.1(0.0–0.1)	1	0.2(0.1–0.2)	106	0.7(0.6–0.9)	342	3.2(2.8–3.5)	796	8.8(8.2–9.4)	4749	20.7(20.2–21.2)
Cerebral/Cardiac	TSC	1	1.1(0.0–5.8)	3	5.1(1.1–14.2)	0	–	9	0.1(0.0–0.1)	2	6.7(0.8–22.1)	0	–	1	5.3(0.1–26.0)
Aneurysm	Comp.	0	–	0	–	6	0.0(0.0–0.1)	0	–	12	0.1(0.0–0.2)	29	0.3(0.2–0.4)	118	0.5(0.4–0.6)
Dermatological															
Angiofibroma	TSC	0	–	2	3.4(0.4–11.7)	4	6.5(1.8–15.7)	6	11.8(4.4–23.9)	1	3.3(0.1–17.2)	2	10.5(1.3–33.1)	0	–
	Comp.	0	–	13	0.0(0.0–0.0)	3	0.0(0.0–0.0)	1	0.0(0.0–0.0)	3	0.0(0.0–0.1)	0	–	6	0.0(0.0–0.0)

(continued on next page)

Table 2A – (continued)

TSC clinical manifestations		<18 yrs[a] TSC n = 94 Comp. n = 18,321		18–25 yrs[a] TSC n = 59 Comp. n = 8326		26–35 yrs[a] TSC n = 62 Comp. n = 15,800		36–45 yrs[a] TSC n = 51 Comp. n = 14,733		46–55 yrs[a] TSC n = 30 Comp. n = 10,834		56–65 yrs[a] TSC n = 19 Comp. n = 9051		>65 yrs[a] TSC n = 19 Comp. n = 22,935	
		n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Benign Skin Neoplasms	TSC	6	6.4(2.4–13.4)	13	22.0(12.3–34.7)	11	17.7(9.2–29.5)	7	13.7(5.7–26.3)	2	6.7(0.8–22.1)	3	15.8(3.4–39.6)	0	–
	Comp.	33	0.2(0.1–0.2)	28	0.3(0.2–0.5)	68	0.4(0.3–0.5)	80	0.5(0.4–0.7)	63	0.6(0.4–0.7)	56	0.6(0.5–0.8)	115	0.5(0.4–0.6)
Impetigo	TSC	10	10.6(5.7–18.7)	7	11.9(5.6–22.8)	8	12.9(6.4–23.7)	3	5.9(1.4–16.5)	1	3.3(0.0–18.1)	2	10.5(1.7–32.6)	0	–
	Comp.	2116	11.6(11.1–12.0)	969	11.6(10.9–12.3)	768	4.9(4.5–5.2)	444	3.0(2.7–3.3)	316	2.9(2.6–3.2)	192	2.1(1.8–2.4)	372	1.6(1.5–1.8)
Lymphoedema	TSC	0	–	0	–	0	–	0	–	0	–	3	15.8(4.7–38.4)	0	–
	Comp.	2	0.0(0.0–0.0)	0	–	2	0.0(0.0–0.0)	12	0.1(0.0–0.1)	8	0.1(0.0–0.1)	17	0.2(0.1–0.3)	73	0.3(0.2–0.4)
Ocular															
Visual impairment	TSC	3	3.2(0.7–9.0)	2	3.4(0.4–11.7)	4	6.5(1.8–15.7)	3	5.9(1.2–16.2)	2	6.7(0.8–22.1)	1	5.3(0.1–26.0)	0	–
	Comp.	31	0.2(0.1–0.2)	31	0.4(0.2–0.5)	61	0.4(0.3–0.5)	70	0.5(0.4–0.6)	87	0.8(0.6–1.0)	113	1.2(1.0–1.5)	1070	4.7(4.4–4.9)
Gastrointestinal System															
Benign Neoplasms/ Polyp of Colon	TSC	0	–	1	1.7(0.0–9.1)	0	–	2	3.9(0.5–13.5)	3	10.0(2.1–26.5)	4	21.1(6.1–45.6)	2	10.5(1.3–33.1)
	Comp.	5	0.0(0.0–0.1)	6	0.1(0.0–0.1)	63	0.4(0.3–0.5)	113	0.8(0.6–0.9)	261	2.4(2.1–2.7)	392	4.3(3.9–4.8)	1269	5.5(5.2–5.8)
Endocrine System															
Hypothyroidism/ Hyperthyroidism	TSC	3	3.2(0.7–9.0)	2	3.4(0.4–11.7)	3	4.8(1.0–13.5)	4	7.8(2.2–18.9)	2	6.7(0.8–22.1)	7	36.8(16.3–61.6)	3	15.8(3.4–39.6)
	Comp.	28	0.2(0.1–0.2)	54	0.6(0.5–0.8)	242	1.5(1.3–1.7)	409	2.8(2.5–3.0)	496	4.6(4.2–5.0)	659	7.3(6.7–7.8)	2304	10.0(9.7–10.4)

[a] Age defined at the point of the last available record for each patient.
[b] ADHD, *Attention deficit hyperactivity disorder*; SEGA, subependymal giant cell astrocytoma; TIA, Transient ischaemic attack.

language disorders, autism spectrum disorders, behavioural disorders, ADHD and learning disability (Fig. 3). In contrast, angiomyolipomas and other kidney neoplasms were diagnosed later in childhood (12.1 [6.6] years of age). Dermatological conditions including benign skin neoplasms and angiofibromas also first presented in childhood (14.5 [4.2] and 16.3 [1.8] years of age, respectively). On average, brain neoplasms (including SEGA) were first diagnosed at 9.4 (6.5) years of age. Suspected cases of lymphangioleiomyomatosis (LAM) were not present in the TSC Birth cohort. However, in the TSC cohort, suspected LAM cases were identified at an average age of 49.4 (26.2) years.

3.5. *Clinical profiles of the TSC cohort*

Further analyses were conducted to better understand the combination of primary organ systems (as defined in MedITOSC) affected in patients with TSC. Each distinct combination was considered a manifestation profile. A total of forty-nine manifestation profiles were identified in the TSC cohort, with 6% of patients having a unique manifestation profile that was not observed in any other patient. In paediatric and adult TSC cohorts, 46% and 62% of patients, respectively, developed clinical manifestations in at least three of the organ systems.

The collective organ system profile of the TSC cohort was represented using a network diagram to illustrate the relationship between organ systems affected and overall disease complexity (Fig. 4). A strong relationship between nervous system, psychiatric and dermatological manifestations was observed in the TSC cohort, partly reflecting a high prevalence of manifestations in each of these organ systems, but also the inherent relationship between brain abnormalities and psychopathology (Fig. 2). The relationship between respiratory, circulatory system and brain (structural) manifestations was the least pronounced in the TSC cohort.

3.6. *TSC cohort mortality*

Data on mortality was examined to ascertain a potential reason for comparatively lower proportion of adult TSC patients versus the Comparator cohort. Analysis of the ONS mortality register showed that only 5% of the TSC cohort (n = 16) had died. These patients had a mean (SD) age at death of 57.5 (20.5) years (median, 61.1 years of age).

4. Discussion

This study is a retrospective, longitudinal analysis of a large cohort of TSC patients in the UK who were treated in general practice. It represents one of the largest population-based studies reporting on this condition. It contributes towards a better understanding of the complexity of this disease and the associated treatment challenges impacting the delivery of patient care in the community setting. Comprehensive data on known TSC manifestations are reported, including their recorded prevalence, age of onset and the different combinations in which they occur, providing further insight into the broad spectrum of TSC clinical profiles.

Table 2B – Prevalence of additional clinical manifestations in the paediatric *vs.* adult TSC population.

TSC clinical manifestations	<18 yrs[a] n = 94		≥18 yrs[a] n = 240	
	n	% (95% CI)	n	% (95% CI)
Brain (Structural)				
Hydrocephalus	3	3.2 (0.7–9.4)	13	5.4 (3.1–9.1)
Psychiatric				
Sleep Disorder	12	12.8 (7.3–21.2)	29	12.1 (8.5–16.9)
Behavioural Disorder	17	18.1 (11.5–27.2)	34	14.2 (10.3–19.2)
Kidney & Urinary Tract				
Haematuria	1	1.1 (0.0–6.4)	20	8.3 (5.4–12.6)
Circulatory System				
Hypertension	0	–	25	10.4 (7.1–15.0)
Arrhythmia	3	3.2 (0.7–9.4)	12	5.0 (2.8–8.6)
Dermatological				
Café au Lait Spots	3	3.2 (0.7–9.4)	0	–
Acne vulgaris/rosacea	1	1.1 (0.0–6.4)	32	13.3 (9.6–18.3)
Naevus	5	5.0 (2.0–12.0)	15	6.0 (4.0–10.0)
Nail Manifestations	5	5.3 (2.0–12.2)	45	18.8 (14.3–24.2)
Skin Tag	0	–	12	5.0 (2.8–8.6)
Respiratory System				
Lymphangioleiomyomatosis (LAM)[b]	0	–	4	1.7 (0.5–4.4)

[a] Age defined at the point of the last available record for each patient.
[b] Suspected cases of LAM only due to unavailability of specific LAM diagnosis codes in CPRD-HES.

Manifestations that are less common in TSC patients, including visual impairment and thyroid disease, have also been described in this study.

The study reflects clinical practice over the time span of the review. A number of complications were recorded at a lower prevalence than one would expect based on small expert research studies[18,21]; the difference is probably likely to represent under-diagnosis, highlighting inadequate care.

A novel approach was taken in the study to categorise all manifestations identified in the TSC cohort resulting in the development of an inventory of clinical codes by organ system, MedITOSC. The development of the inventory was a critical first step in the study to support all subsequent analyses and has the potential to evolve over time as more clinical data on TSC patients becomes available and can be used to support future TSC studies planned in the CPRD-HES databases.

All patient records available in the CPRD-HES (~7 million) were used to identify a diagnosis record for TSC. Based on an estimated population prevalence of 1/20,000 of diagnosed TSC,[14,15,18] the expected number of patients in the CPRD-HES was approximately 350 patients. The current study identified 334 TSC patients, which is consistent with the expected number in the general CPRD-HES population. However, additional reports have estimated the prevalence of TSC at 1/11,000, taking into account undiagnosed cases.[14] This suggests that there are a similar number of TSC patients in the CPRD-HES without a recorded diagnosis. The demographic findings support this hypothesis but also raise questions around a potentially higher impact of TSC on mortality than previously documented.[30] The TSC patient cohort had a distribution of gender and available history that was consistent with the Comparator cohort. However, the age distribution of patients differed substantially between cohorts, with a smaller proportion of older patients observed in the TSC cohort versus the Comparator cohort (11% *vs.* 31% of subjects over 55 years of age). This under-representation of older adults in the CPRD-HES could reflect historical under-diagnosis of TSC, older patients seeking care in alternative facilities not captured in CPRD-HES, or a loss to follow-up during the transition to adulthood due to a lack of coordinated care.

This study reports the prevalence of TSC manifestations and contrasts this against the prevalence in the general CPRD population. The most common manifestations were dermatological and nervous system manifestations (predominantly epilepsy). These were markedly more frequent than in the Comparator cohort at all age intervals and concur with previous reports,[31–34] although others have reported an even higher prevalence of epilepsy (85%) in the setting of a specialist TSC clinic.[35] The prevalence of angiofibromas were lower than expected.[18,19] This could be due to misdiagnosis of acne vulgaris or rosacea due to physicians lack of familiarity with TSC and related dermatological manifestations in general practice. A high occurrence of lymphoedema was noted in the 45–65 year age interval but no TSC patients were diagnosed outside of this age band. While an association has previously been suggested,[36] our data are not able to offer any additional insights on this particular association. The apparent increased prevalence of impetigo in adults with TSC has not been described previously and is likely to be associated with other TSC-related dermatological manifestations, or may result from poor hygiene and subsequent susceptibility to infection.

As anticipated, the TSC cohort had a higher prevalence of brain neoplasms (including SEGA) with 11% of paediatric TSC patients affected compared with 0% in the Comparator cohort. Epilepsy and brain neoplasms (including SEGA) are

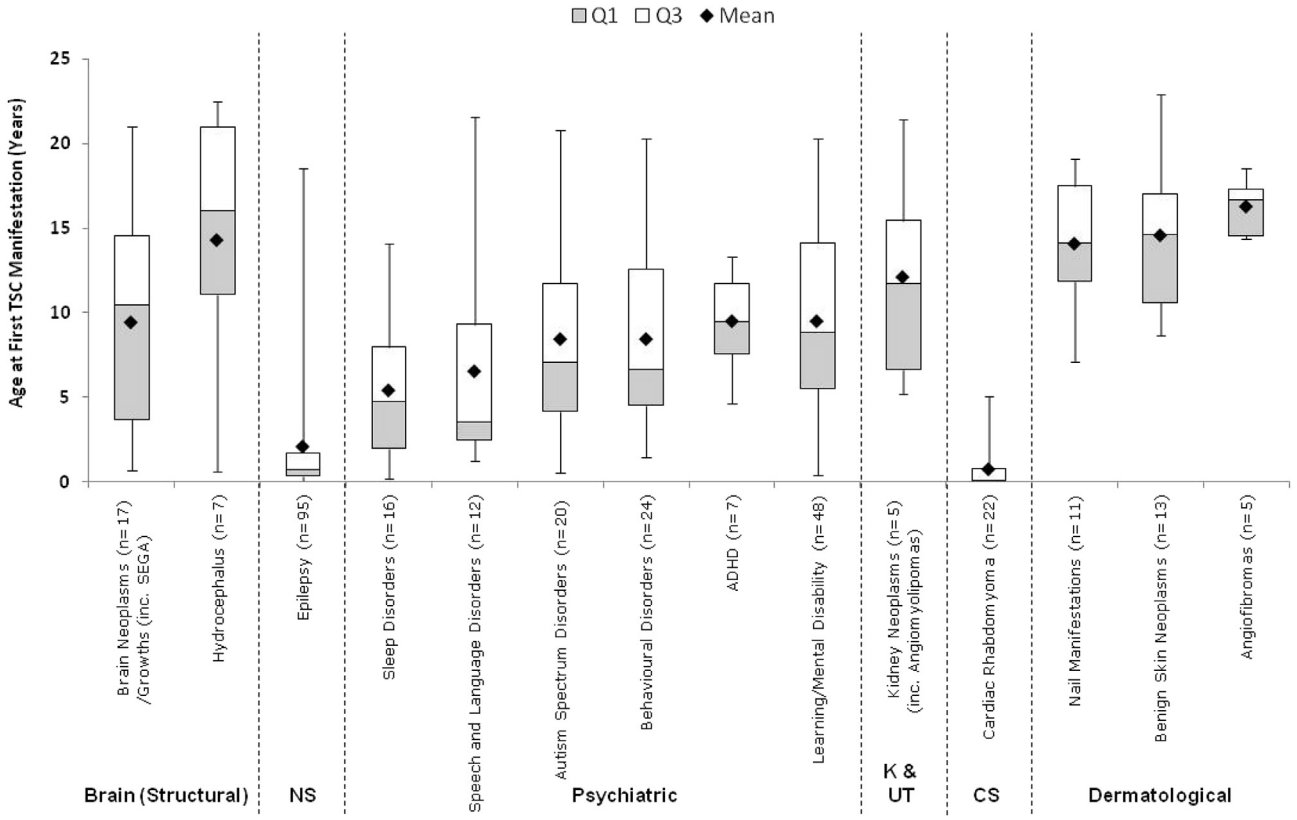


Fig. 3 – A box plot showing the variation in age of TSC patients at first diagnosis record for select clinical manifestations (n ≥ 5) by primary organ system. Analyses were conducted in the sub-population of TSC patients for whom records were available from birth; TSC Birth cohort (n = 124). NS, Nervous System; K & UT, Kidney and Urinary Tract; CS, Circulatory System.

known to pose a risk of serious neurological complications.[37] Epilepsy has been strongly linked to learning/intellectual disability,[35,38,39] and has a detrimental impact on patient quality of life[40,41]; consequently, epilepsy should be the subject of vigilant surveillance in all patients with suspected TSC. This agrees with our findings surrounding the combination of organ systems affected in the TSC cohort, which demonstrated a strong relationship between nervous system and psychiatric manifestations, with further association of brain (structural) manifestations. Vigilant monitoring of patients will result in earlier detection of these manifestations, allowing interventions to be administered sooner. In turn, this will mitigate the risk of developing more severe complications later in life, which are harder to treat and have a higher clinical burden.

Psychiatric manifestations were seen in over half of paediatric (55%) and adult (68%) TSC patients, consistent with previous estimates (~40–80%).[42] The high prevalence, which increased with age, highlights the importance of psychiatric referral and the need for a coordinated approach to improve the quality and efficiency of care. Intellectual disability was observed in over one-third of children with TSC (compared with 1% in the general CPRD population). Similarly, autism spectrum disorders (16%) and ADHD (7%) also develop more frequently in paediatric TSC patients compared with the Comparator cohort. However, prior research has typically reported higher prevalence estimates for these conditions.[43–45] The lower prevalence in our TSC cohort might be explained by under-reporting of these conditions in general practice as they are not routinely sought, further highlighting the need for more systematic psychiatric assessment in TSC.

The kidney and urinary tract are also commonly affected in TSC, with angiomyolipomas and simple renal cysts developing with increasing prevalence over the course of the disease.[38,46,47] Severe early onset of polycystic kidney disease has been associated with contiguous *TSC2* and *PKD1* gene deletions.[48] Our findings were consistent with these reports and notably, the prevalence of CKD stage 3–5 observed in adult TSC patients (30%–42%) over the age of 45 years was markedly higher than that reported in the Comparator cohort (3%–23%). Also noteworthy was a higher occurrence of stroke/TIA accompanying the increase in CKD stage 3–5 prevalence in the TSC cohort. Stroke/TIA may have occurred as a direct result of hypertension, known to develop in patients with CKD.[49] The high rates of CKD stage 3–5 are likely a consequence of the late detection and poor management of earlier angiomyolipomas and renal cysts and, thus, strongly supports the current TSC clinical guidelines for diagnosis and surveillance recommending regular assessment of renal function.[18,21] Our data suggest that CKD stage 3–5 is a more frequent complication of TSC than previously understood and may contribute to substantial morbidity in adulthood.

The lungs of adults with TSC, particularly women, are frequently affected by LAM, a cystic lung disease that is an

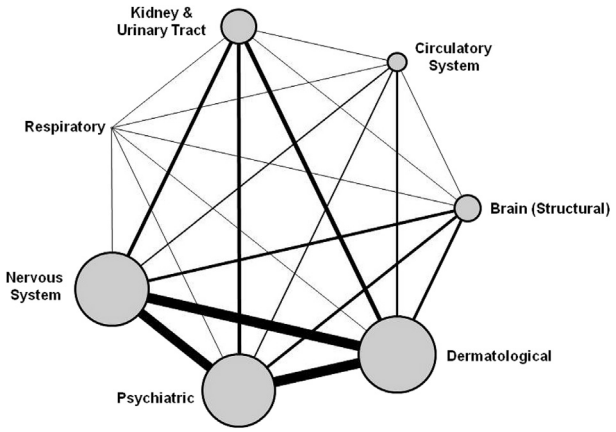


Fig. 4 – In order to demonstrate the broad spectrum of manifestation profiles (TSC-related and TSC-associated) in the TSC cohort, the number of primary organ systems affected for each patient was explored and presented as a network diagram (n = 324). The relative size of each node reflects the frequency of organ system involvement while the width of each connecting line (between nodes) reflects the frequency of patients that have manifestations involving both these organ systems. The most common manifestation profile observed was patients with nervous system, skin and psychiatric manifestations (21%). Theoretically, the number of possible different individual presentations is 7^7 at organ system level. However, there are still many different combinations of manifestations in TSC. Note: 7 patients in the TSC cohort did not develop a clinical manifestation within any of the seven primary organ systems.

increasingly important cause of morbidity and death in adults with TSC.[50] The low prevalence of respiratory disease in our TSC cohort is striking since screening studies have shown that lung cysts are present in 27% of women at 21 years and 80% of women at 40 years.[51] LAM symptoms are frequently attributed to more common diseases including asthma and COPD[52] and our data suggest that LAM may have been overlooked in our cohort, with only 'suspected' cases of LAM identified. An early diagnosis of LAM may prevent complications and disability[53]; adoption of the recent TSC management guidelines, which recommend screening adult women for LAM by computerised tomography scanning, should improve recognition of LAM.[21]

Several manifestations were also observed in other organ systems that are not well recognised as being affected by TSC, including those in the endocrine and gastrointestinal systems[13,18–20]

Manifestations reported in these particular organ systems were higher compared with the Comparator cohort, providing preliminary frequency data for these under-reported features as well as suggesting that they may be TSC-related. Of note was the higher prevalence of hypothyroidism/hyperthyroidism in the TSC cohort when compared with the Comparator cohort, especially later in adulthood. Only a few studies have previously reported abnormalities of the thyroid gland in TSC patients.[27,54] Paediatric and adult TSC patients were also shown to have developed visual impairment more frequently than in the Comparator cohort, another manifestation that has been explored less often in TSC. Such manifestations may be under-reported in real clinical practice due to psychiatric complications (e.g. intellectual disability) affecting surveillance and adequate care of patients as well as the ability to effectively communicate their symptoms; hyperactive and/or autistic features may also aggravate this problem. Previous studies have reported that the development of retinal astrocytic hamartomas may rarely affect vision,[55] while raised intracranial pressure due to progressing SEGAs is a well recognised cause of visual loss in TSC.[56] Retinal side effects associated with vigabatrin use for the treatment of seizures have also been reported.[21]

Whilst TSC is known to involve multiple organ systems, most published studies analyse only a single organ system. This study highlights the complexity of TSC by reporting the collective organ system profile of the TSC cohort. Forty-nine different manifestation profiles by primary organ system were identified within the TSC cohort (meaning considerably more clinical profiles exist at the individual manifestation level), with approximately half of paediatric and adult TSC patients having involvement of three or more organ systems. Considering the seven nodes in the network diagram (Fig. 4) gives a mathematical possibility of 7^7 (823,543) different combinations of organ system manifestations. In practice, this finding underlines the enormous phenotypic variety in TSC that makes management so complex. This lends considerable weight to the requirement for a holistic and coordinated management approach in order to deliver efficient and effective care for TSC patients throughout their lifetime.

A strength of this study lies in the large cohort of TSC patients derived from the CPRD-HES, for whom available history, on average, spanned almost two decades and the inclusion of a substantial proportion for whom data was available from birth. A further strength was the capture of data from both primary and secondary health care settings. This has enabled a greater understanding of the development of clinical manifestations over time (including those less frequently associated with TSC) and has allowed differences in the prevalence of manifestations in both paediatric and adult patients to be examined. Furthermore, comprehensive review of each TSC patient record by a number of clinical experts (resulting in the development of MedITOSC) has validated TSC and manifestation diagnoses as well as contributing more broadly to interpretation. Finally, the CPRD has been shown to cover a representative sample of patients in the UK[22,25] and thus, findings from this source are believed to be generalisable to the national TSC population, with the caveat that many complications are likely to be under-diagnosed.

The shortcomings of this study are typical for retrospective database studies, where data are limited by the level of detail and quality of information recorded. For example, accident and emergency visits are only reported in the CPRD-HES if they result in a subsequent admission into hospital. Another example is that the lack of a specific code for common TSC manifestations (e.g. hypomelanotic lesions, retinal hamartomas, cerebral tubers) means that these are either not recorded or possibly misreported. Additionally, the

linkage of the CPRD and HES databases was only available for part of the study period, suggesting that patients may have experienced additional events and diagnoses in specialist care that we were unable to report (especially in the outpatient setting). The manifestations reported in this survey are a mixture of clinical problems for which patients sought medical advice and some chance findings, representative of TSC care in a primary practice. Routine surveillance has generally been non-systematic in the UK and most patients are not followed-up in TSC clinics; this may partially explain some differences in prevalence of non-symptomatic lesions (e.g. renal angiomyolipomas) reported for this population and smaller intensively studied groups of patients from specialised TSC centres.[33] The prevalence of some manifestations is likely to be under-reported, particularly those that normally develop later in life, considering the relatively young age of the TSC cohort in the CPRD-HES, or for those manifestations where specific diagnosis codes are unavailable (e.g. LAM). In addition, it is likely that some patients with TSC are not captured in the CPRD-HES due to under- or misdiagnosis of this disease. Furthermore, the low mortality in the TSC cohort is likely to be under-reported due to the younger age of the study population. Lastly, this study does not include information from the mental health and social care settings and will, therefore, not capture all care administered to TSC patients with psychiatric disorders.

This study has highlighted several areas that may warrant further investigation. Firstly, given the under-representation of adults in this particular TSC cohort, it would be beneficial to explore the care pathways of adult TSC patients in the UK. This would support a greater understanding of the health care settings utilised by these patients, and identify both potential points of sub-optimal care and those points at which patients are lost to follow-up. Secondly, a study that aims to establish the economic burden of TSC in the UK would provide additional insights in relation to the clinical findings reported for the current study. Thirdly, considering the higher prevalence of CKD stage 3–5 reported in our TSC cohort versus the general CPRD population, future studies are required to delineate the causes and effectiveness of treatment options for CKD in TSC to prevent major morbidity. Finally, further studies to confirm preliminary findings of greater occurrence of visual impairment, thyroid disease, impetigo and lymphoedema in TSC would also be of benefit.

5. Conclusion

To the authors' knowledge, this represents one of the largest TSC cohort studies undertaken in the general population and highlights the substantial burden of this genetic disorder in the UK. The study demonstrates the complex nature of TSC, with patients presenting with a broad spectrum of manifestation profiles that evolve over time. Recent clinical guidelines aimed at improving diagnosis, clinical surveillance and management of TSC[18,21] provide a benchmark against which current practice and service provision can be measured and support the need for a coordinated care approach to improve long-term health outcomes for patients with TSC.

Author contributions

All authors supported final study conception and design, analysis and interpretation of the data, revising the article critically for important intellectual content and final approval of the published version.

Funding

This research was funded by Novartis Pharmaceuticals.

Conflicts of interest

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article:

Authors EG, MM and AP are employees of Novartis Pharmaceuticals. Authors DD, LL and PN are employees of IMS Health, a consulting company that received funding from Novartis to conduct this study. Authors PB, SJ, CK and JRS have received honoraria from Novartis. CK and JRS have also worked as principal investigators on studies that were funded or part-funded by Novartis. Authors PC, CH and CS have no conflicts of interest with respects to the research and manuscript. Author JS is chief executive of the Tuberous Sclerosis Association (TSA); the TSA has received grant funding from Novartis.

REFERENCES

1. van Slegtenhorst M, de Hoogt R, Hermans C, et al. Identification of the tuberous sclerosis gene *TSC1* on chromosome 9q34. *Science* 1997;**277**(5327):805–8.
2. European Chromosome 16 Tuberous Sclerosis Consortium. Identification and characterization of the tuberous sclerosis gene on chromosome 16. *Cell* 1993;**75**(7):1305–15.
3. Huang J, Dibble C, Matsuzaki M, Manning B. The TSC1-TSC2 complex is required for proper activation of mTOR complex 2. *Mol Cell Biol* 2008;**28**(12):4104–15.
4. Kozlowski P, Roberts P, Dabora S, et al. Identification of 54 large deletions/duplications in *TSC1* and *TSC2* using MLPA, and genotype–phenotype correlations. *Hum Genet* 2007;**121**(3–4):389–400.
5. Au KS, Williams AT, Roach ES, et al. Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis complex in the United States. *Genet Med* 2007;**9**(2):88–100.
6. Dabora SL, Jozwiak S, Franz DN, et al. Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. *Am J Hum Genet* 2001;**68**(1):64–80.
7. Jones AC, Shyamsundar MM, Thomas MW, et al. Comprehensive mutation analysis of *TSC1* and *TSC2*—and phenotypic correlations in 150 families with tuberous sclerosis. *Am J Hum Genet* 1999;**64**(5):1305–15.
8. Niida Y, Lawrence-Smith N, Banwell A, et al. Analysis of both TSC1 and TSC2 for germline mutations in 126 unrelated patients with tuberous sclerosis. *Hum Mutat* 1999;**14**(5):412–22.

9. Sancak O, Nellist M, Goedbloed M, et al. Mutational analysis of the TSC1 and TSC2 genes in a diagnostic setting: genotype–phenotype correlations and comparison of diagnostic DNA techniques in tuberous sclerosis complex. *Eur J Hum Genet* 2005;**13**(6):731–41.
10. Crino P, Nathanson K, Henske E. The tuberous sclerosis complex. *N Engl J Med* 2006;**355**(13):1345–56.
11. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. *Ann N Y Acad Sci* 1991;**615**:125–7.
12. Astrinidis A, Henske EP. Tuberous sclerosis complex: linking growth and energy signaling pathways with human disease. *Oncogene* 2005;**24**(50):7475–81.
13. Rosser T, Panigrahy A, McClintock W. The diverse clinical manifestations of tuberous sclerosis complex: a review. *Semin Pediatr Neurol* 2006;**13**(1):27–36.
14. O'Callaghan FJ, Shiell AW, Osborne JP, Martyn CN. Prevalence of tuberous sclerosis estimated by capture-recapture analysis. *Lancet* 1998;**351**(9114):1490.
15. Sampson J, Scahill S, Stephenson J, Mann L, Connor J. Genetic aspects of tuberous sclerosis in the west of Scotland. *J Med Genet* 1989;**26**(1):28–31.
16. Webb D, Clarke A, Fryer A, Osborne J. The cutaneous features of tuberous sclerosis: a population study. *Br J Dermatol* 1996;**135**(1):1–5.
17. Harris-Stith R, Elston DM. Tuberous sclerosis. *Cutis* 2002;**69**(2):103–9.
18. Northrup H, Krueger DA. International tuberous sclerosis complex consensus group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 international tuberous sclerosis complex consensus conference. *Pediatr Neurol* 2013;**49**(4):243–54.
19. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. *Lancet* 2008;**372**:657–68.
20. Seri S, Cerquiglini A, Pisani F, Curatolo P. Autism in tuberous sclerosis: evoked potential evidence for a deficit in auditory sensory processing. *Clin Neurophysiol* 1999;**110**(10):1825–30.
21. Krueger DA, Northrup H, International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 international tuberous sclerosis complex consensus conference. *Pediatr Neurol* 2013;**49**(4):255–65.
22. Williams T, van Staa T, Puri S, Eaton S. Recent advances in the utility and use of the general practice research database as an example of a UK primary care data resource. *Ther Adv Drug Saf* 2012;**3**(2):89–99.
23. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the general practice research database: a systematic review. *Br J Gen Pract* 2010;**60**(572):128–36.
24. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the general practice research database: a systematic review. *Br J Clin Pharmacol* 2010;**69**(1):4–14.
25. García Rodríguez LA, Pérez Gutthann S. Use of the UK general practice research database for pharmacoepidemiology. *Br J Clin Pharmacol* 1998;**45**(5):419–25.
26. Clarson LE, Hider SL, Belcher J, et al. Increased risk of vascular disease associated with gout: a retrospective, matched cohort study in the UK clinical practice research datalink. *Ann Rheum Dis* 2014;**74**(4):642–7.
27. Anandarajah S, Tai T, de Lusignan S, Stevens P, O'Donoghue D, Walker M, Hilton S. The validity of searching routinely collected general practice computed data to identify patients with chronic kidney disease (CKD): a manual review of 500 medical records. *Nephrol Dial Transpl* 2005;**20**(10):2089–96.
28. Fombonne E, Heavey L, Smeethh L, Rodrigues LC, Cook C, Smith PG, Meng L, Hall AJ. Validation of the diagnosis of autism in general practitioner records. *BMC Public Health* 2004;**4**(5). http://dx.doi.org/10.1186/1471-2458-4-5.
29. Kwiatkowski DJ, Whittemore VH, Thiele EA. *Tuberous sclerosis complex: genes, clinical features, and therapeutics*. Wiley Blackwell; 2010, ISBN 978-3-527-32201-5. p. 372.
30. Tuberous Sclerosis Fact Sheet. National Institute of Neurological Disorders and Stroke. 11 April 2006. Retrieved 3rd Oct 2006.
31. Wataya-Kaneda M, Tanaka M, Hamasaki T, Katayama I. Trends in the prevalence of tuberous sclerosis complex manifestations: an epidemiological study of 166 Japanese patients. *PLoS One* 2012;**8**(5):e63910.
32. Teng JM, Cowen EW, Wataya-Kaneda M, et al. Dermatologic and dental aspects of the 2012 International Tuberous Sclerosis Complex Consensus statements. *JAMA Dermatol* 2014;**150**(10):1095–101.
33. Yates JR, Maclean C, Higgins JN, et al., Tuberous Sclerosis 2000 Study Group. The tuberous sclerosis 2000 study: presentation, initial assessments and implications for diagnosis and management. *Arch Dis Child* 2011;**96**(11):1020–5.
34. Vignoli A, La Briola F, Turner K, et al. Epilepsy in TSC: certain etiology does not mean certain prognosis. *Epilepsia* 2013;**54**(12):2134–42.
35. Chu-Shore CJ, Major P, Camposano S, Muzykewicz D, Thiele EA. The natural history of epilepsy in tuberous sclerosis complex. *Epilepsia* 2010;**51**(7):1236–41.
36. Geffrey AL, Shinnick JE, Staley BA, Boronat S, Thiele EA. Lymphedema in tuberous sclerosis complex. *Am J Med Genet A* 2014;**164A**(6):1438–42.
37. Jozwiak S, Nabbout R, Curatolo P, TSC Consensus Meeting for SEGA and Epilepsy Management. Management of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC): clinical recommendations. *Eur J Paediatr Neurol* 2013;**30**:1–5.
38. O'Callaghan FJ, Noakes MJ, Martyn CN, Osborne JP. An epidemiological study of renal pathology in tuberous sclerosis complex. *BJU Int* 2004;**94**(6):853–7.
39. van Eeghen AM, Pulsifer MB, Merker VL, et al. Understanding relationships between autism, intelligence, and epilepsy: a cross-disorder approach. *Dev Med Child Neurol* 2013;**55**(2):146–53.
40. de Vries P. Neurodevelopmental, psychiatric and cognitive aspects of tuberous sclerosis complex. In: Kwiatkowsi DJ, Whitte- more VH, Thiele EA, editors. *Tuberous sclerosis complex*. Weinheim, Germany: Wiley-Blackwell; 2010. p. 229–68.
41. Krueger DA, Wilfong AA, Holland-Bouley K, et al. Everolimus treatment of refractory epilepsy in tuberous sclerosis complex. *Ann Neurol* 2013;**74**(5):679–87.
42. Muzykewicz DA, Newberry P, Danforth N, Halpern EF, Thiele EA. Psychiatric comorbid conditions in a clinic population of 241 patients with tuberous sclerosis complex. *Epilepsy Behav* 2007;**11**(4):506–13.
43. Chung TK, Lynch ER, Fiser CJ, et al. Psychiatric comorbidity and treatment response in patients with tuberous sclerosis complex. *Ann Clin Psychiatry* 2011;**23**(4):263–9.
44. Bolton PF, Park RJ, Higgins JN, Griffiths PD, Pickles A. Neuro-epileptic determinants of autism spectrum disorders in tuberous sclerosis complex. *Brain* 2002;**125**:1247–55.
45. Leclezio L, Jansen A, Whittemore VH, de Vries PJ. Pilot validation of the tuberous sclerosis-associated neuropsychiatric disorders (TAND) checklist. *Pediatr Neurol* 2015;**52**(1):16–24.
46. Dixon BP, Hulbert JC, Bissler JJ. Tuberous sclerosis complex renal disease. *Nephron Exp Nephrol* 2011;**118**:e15–20.
47. Bissler JJ, Kingswood JC. Renal angiomyolipomata. *Kidney Int* 2004;**66**(3):924–34.

48. Brook-Carter PT, Pearl B, Ward CJ, et al. Deletion of the TSC2 and PKD1 genes associated with severe infantile polycystic kidney disease—a contiguous gene syndrome. *Nat Genet* 1994;**8**(4):328–32.
49. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013;**382**(9889):339–52.
50. Seibert D, Hong C-H, Takeuchi F, et al. Recognition of tuberous sclerosis in adult women: delayed presentation with life-threatening consequences. *Ann Intern Med* 2011;**154**:806–13.
51. Cudzilo CJ, Szczesniak RD, Brody AS, et al. Lymphangioleiomyomatosis screening in women with tuberous sclerosis. *Chest* 2013;**144**(2):578–85.
52. Cohen MM, Pollock-BarZiv S, Johnson SR. Emerging clinical picture of lymphangioleiomyomatosis. *Thorax* 2005;**60**:875–9.
53. Johnson SR, Cordier JF, Lazor R, et al. European respiratory society guidelines for the diagnosis and management of lymphangioleiomyomatosis. *Eur Respir J* 2010;**35**:14–26.
54. Adhvaryu K, Shanbag P, Vaidya M. Tuberous sclerosis with hypothyroidism and precocious puberty. *Indian J Pediatr* 2004;**71**(3):273–5.
55. Shields JA, Eagle Jr RC, Shields CL, Marr BP. Aggressive retinal astrocytomas in four patients with tuberous sclerosis complex. *Trans Am Ophthalmol Soc* 2004;**102**:139–47.
56. Pascual-Castroviejo I, Pascual-Pascual SI, Velázquez-Fragua R, et al. Subependymal giant cell astrocytoma in tuberous sclerosis complex. A presentation of eight paediatric patients. *Neurologia* 2010;**25**(5):314–21.